Seizure 22 (2013) 522–527

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

# Epileptic prodromes: Are they nonconvulsive status epilepticus?

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ARTICLE INFO

*Article history:*
Received 12 February 2013
Received in revised form 26 March 2013
Accepted 27 March 2013

*Keywords:*
EEG
Epilepsy prodrome
Nonconvulsive status epilepticus

ABSTRACT

*Purpose:* The aim of this study was to assess how frequently prodromes occur in an adult patient group from a tertiary referral epilepsy centre and to investigate the EEG changes during the prodromes.
*Methods:* 578 consecutive patients were interviewed on subjective phenomena, experiences heralding the seizures, for at least 30 min before the start of the seizure. EEGs were recorded during the prodromes.
*Results:* Ten out of 490 included patients had prodromes (2%). We were able to record EEG during prodromes in 6 patients. Three patients had EEG changes corresponding to nonconvulsive status epilepticus. Three patients had unrevealing EEG recordings during prodromes.
*Conclusion:* Our results suggest that at least in a part of the patients, the prodromes are actually ictal phenomena, and should be treated as nonconvulsive status epilepticus.


## 1. Introduction

Since ancient times premonitory (warning) symptoms preceding epileptic seizures have been described, and referred to as prodromes (from Greek prodromos, which means forerunning).[1] Two main subgroups have been mentioned in the literature[2]: observable changes in patient behaviour (dysphoria/depression, aggressiveness, slowing of cognitive performance) and subjective experiences (mood changes, strange sensations, "distant feeling" or somatosensory or specific sensory experiences), which build up to the seizure.

Blumer and Altschuler describe the phenomenon in the following way[3]: "The prodromata or premonitory symptoms of seizures are of a prolonged nature and can be clearly distinguished from the highly stereotyped (though often complex) primictal events referred to as auras, whose duration can be usually estimated in seconds. The literature is almost bare of references to the epileptic prodrome. The prodromal symptoms of seizures deserve more attention than they have received in the literature. They tend to be relatively stereotyped for a given patient and can serve as reliable warning of an approaching seizure".

In the ILAE proposal for a Glossary of Terms for ictal events,[4] prodromes are described as "a subjective or objective clinical alteration (e.g. ill-localized sensation or agitation) that heralds the onset of an epileptic seizure but does not form part of it". Unfortunately the authors do not specify criteria for excluding or including a phenomenon as part of the seizure.

In the literature, references to systematic studies of prodromes are sparse (Taylor, 2007[5])), but anecdotal descriptions of these phenomena abound.

How frequently prodromes occur is much a subject of debate in the literature. In a number of studies, the percentage of patients reporting prodromes vary widely (between 6 and 39%); however, most studies have given figures about 10%.[6–11]

Possible pathophysiological mechanisms underlying prodromes have received scant attention, and only one case report included EEG findings recorded during prodromal manifestations.[12]

From a clinical point of view, prodromes are important also because of their potential therapeutic implications. Patients experiencing prodromes reported that they could abort or prevent their seizures, and it was suggested that additional pharmacological and behavioural interventions are beneficial in this pre-ictal stage.[7,8,11,13]

Having observed in our hospital a case of prodromes, which turned out to be nonconvulsive status epilepticus (NCSE), we planned a prospective study with the following two aims[1]: to assess how frequently prodromes occur in an adult patient group from a tertiary referral epilepsy centre[2]; to investigate whether the prodromes were in fact manifestations of nonconvulsive status epilepticus.

## 2. Methods

At the Danish Epilepsy Centre (a national, tertiary referral centre for patients with epilepsy), in the period August 2004 – July

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http://dx.doi.org/10.1016/j.seizure.2013.03.013

2005, all adult (older than 18-years) patients were interviewed for possible premonitory phenomena, using a structured interview scheme (questionnaire), by the attending physicians. The study was approved by the regional Scientific Ethics Committee, and the patients gave their informed consent.

The patients were systematically asked about any personally experienced premonitory symptoms of emotional, cognitive or sensory character which lasted for an estimated minimum of 30 min before the start of habitual seizures. The questionnaire provided hints to a number of core symptoms in prodromes (irritability, sadness, depression, fear, anger, elation, feeling of exhaustion, headache, confusion, disorientation, speech disturbance, urge to urinate or defaecate, weird feeling difficult to describe).

When patients mentioned in the questionnaire premonitory symptoms lasting longer than 30 min before the start of the habitual seizure, one of the investigators (JA) performed a second evaluation of their symptoms through either a face-to-face or telephone interview. The patients were considered to have prodromes when: (1) they had a diagnosis of epilepsy, confirmed in our centre; (2) reported premonitory subjective symptoms lasting continuously for at least 30 min before the start of the habitual seizures; (3) the premonitory symptoms were different from the patient's aura (if any).

Exclusion criteria: seizure-free for more than six months prior to evaluation; patients experiencing psychogenic non-epileptic seizures (PNES) or significant psychiatric co-morbidity (including mental retardation/dementia, autism).

Patients with prodromes were offered the possibility to contact our department any time in order to record an acute EEG during the episodes with prodromes.

## 3. Results

Questionnaires were filled in by 578 patients. Eighty-eight patients were excluded, based on the criteria specified in methods. Thus, totally 490 patients were evaluated for the occurrence of prodromic phenomena (supplementary material 1). Ten patients (2%) fulfilled our criteria for prodromes.

Out of the 351 patients with focal epilepsy, 7 patients had prodromes (2%). Out of the 91 patients with generalised epilepsy, 3 patients had prodromes (3%). Forty-eight patients could not be classified as focal or generalised. There was no significant difference in the occurrence of prodromes between the patients with focal and generalised epilepsy (Chi-squared test; $p = 0.86$).

The patients experienced several symptoms during the prodromic period (Table 1).

In case 1 and 2, additional administration of AEDs was able to abort the occurrence of GTCS to a high degree. Among all 10 patients, 50% had all their seizures preceded by prodromes, whereas only in 2, prodromes were invariably followed by seizures.

EEG was recorded during prodromes in 6 patients. Three patients had EEG with continuous or waxing and waning paroxysmal activity, indicating nonconvulsive status epilepticus. Figs. 1–3 and supplementary material 2–4 show EEG changes during prodromes compared with the interictal EEG. Supplementary material 5 contains details on the clinical data and EEG findings of the six patients who had EEG recordings during prodromes.

**Table 1**
Symptoms during the prodromes.

| Patient number | Prodromic symptoms |
|---|---|
| 1 | Strange body sensation |
| | Vegetative changes: sweating, palpitation |
| 2 | Irritability |
| | Fatigue |
| | Difficulties in concentration |
| 3 | Nausea |
| | Feeling of "remoteness" |
| 4 | Restlessness/agitation |
| | Strange body sensation/bilateral paraesthesiae |
| 5 | Strange body sensation: out-of-body experience |
| | Feeling of head spit into two |
| 6 | Feeling of "remoteness" |
| | Sadness |
| | Emotional instability |
| | Headache |
| 7 | Fear |
| | Out-of-body experience |
| 8 | Dysphoria |
| | Feeling of swelling of the testes |
| 9 | Feeling of "remoteness" |
| | Dizziness |
| | Difficulties in concentration |
| 10 | Palpitation |
| | Agitation/anxiety |

## 4. Discussion

The prevalence of patients with epilepsy who experience prodromes was 2% in our study. This is below the previously published figures, which are between 6 and 39%. This is probably due to different definition of prodromes used in these studies and the method of patient selection. The two studies[7,8] showing the highest occurrence of prodromes (39% and 29%) included both subjective features and observable behavioural alterations, whereas the other previous studies (as well as ours) only addressed subjective experiences as the entrance criteria.

We opted for the more restrictive definition of prodromes to comply with the ILAE glossary of terms.[4] Auras (independent of their duration) were excluded because they undoubtedly are part of the seizure. In addition, we chose not to include patients with observable signs, as it would have been difficult (arbitrary) to differentiate them from the ictal phenomena. Excluding premonitory symptoms identical with the patient's aura and the observable signs might have decreased the sensitivity, explaining the lower rate of occurrence in our study compared to the previously published ones. However, clearly differentiating prodromes from prolonged initial ictal phenomena was necessary in order to obtain a high specificity for the neurophysiological study. Thus, the EEG findings in our patients cannot be merely attributed to a prolonged initial ictal phase. In addition, to avoid false-positive findings, we excluded from our study patients who also had PNES or other psychiatric co-morbidities.

We were able to record EEG during the prodromes in 6 patients. EEG changes corresponding to nonconvulsive status epilepticus were present in 3 patients.[14] In all three cases the prodromal phenomena fulfilled the criteria given by the ILAE Task Force on Classification and terminology–namely "a subjective or objective clinical alteration (e.g. ill-localized sensation or agitation) that heralds the onset of an epileptic seizure but does not form part of it".[2] This definition is in accordance with the description given by Blumer and Altschuler.[3] Both prodromal symptoms and the EEG abnormalities responded well to acute treatment with benzodiazepines, further emphasising the ictal character of the prodromal phenomena.

A previously published case report described epileptiform discharges, periodic lateralised epileptiform discharges (PLEDs) associated to prodromal symptoms, in three patients.[12] EEG was interpreted as expression of nonconvulsive status epilepticus.

In our series of systematically selected patients with prodromal symptoms, half of the patients who had EEG recorded during


**Fig. 1.** Generalised, 1.5–2 Hz paroxysmal activity, interspersed with runs of 4–5 Hz "notched" theta, mainly bifrontal, and without any focal traits (A). The paroxysmal activity did not respond to intravenous VPA (2200 mg); 10 min later, DZP (5 mg) was given i.v. and the EEG normalised within 30 s (B). EEG is showed here in longitudinal bipolar montage. Supplementary material 2 shows the same EEG segments in common average montage. The patient has symptomatic focal epilepsy (left frontal meningioma).

prodromes showed findings consistent with nonconvulsive status epilepticus. PLEDs were not seen.

Simple focal seizures may not always be manifest in the scalp EEG, and especially non-motor seizures are often EEG negative.[15] Thus, we cannot rule out that more of our patients with acute EEG recorded in fact have NCSE.

The recognition of prodromes as a manifestation of NCSE has obvious therapeutical implications, as it makes it possible to abort

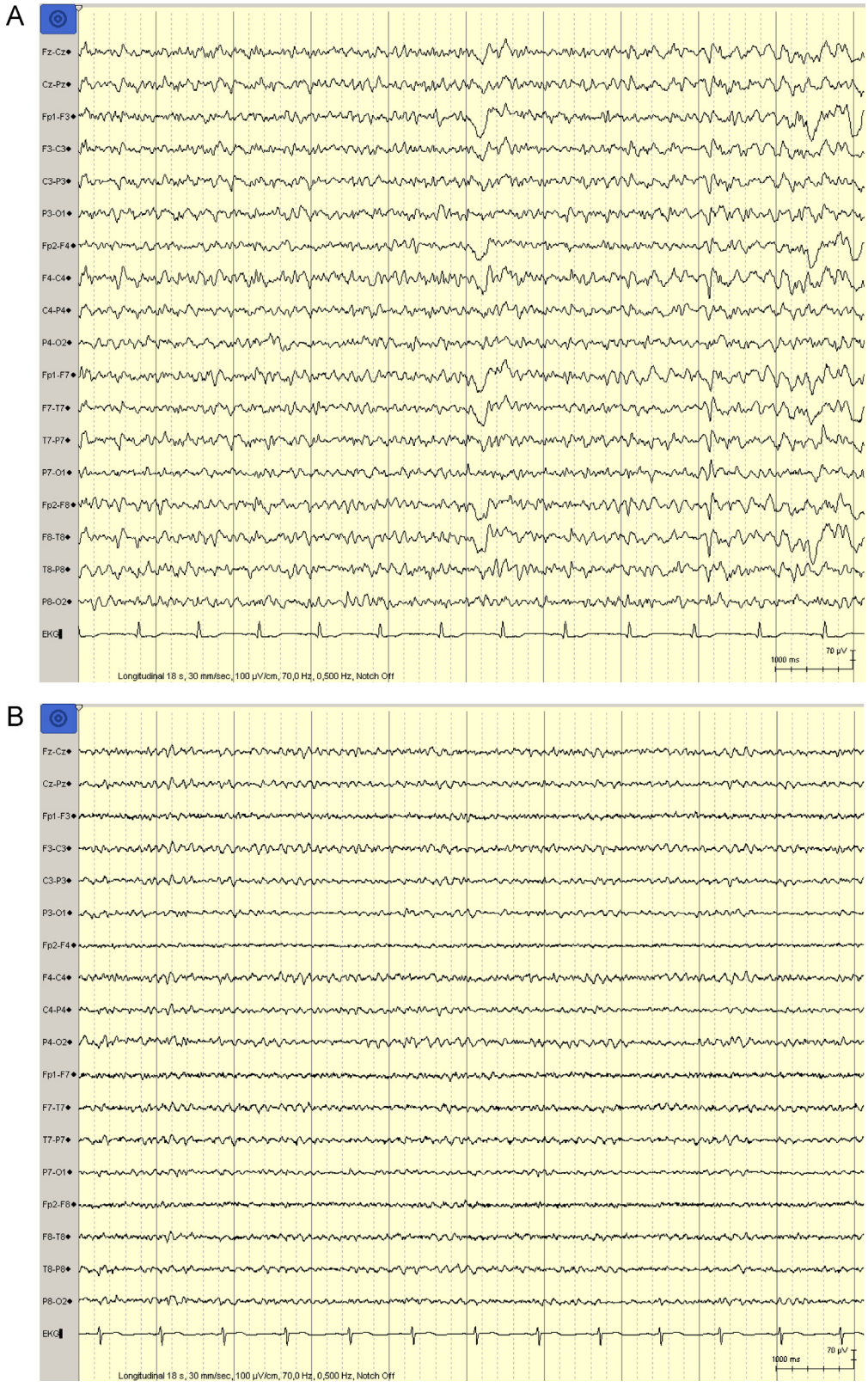


**Fig. 2.** Continuous, diffuse 5–7 Hz activity, with occasional sharp-waves in the left and right posterior quadrant (A). Eye closing/opening induced no alteration. Injection of 1 mg clonazepam i.v. improved the background activity considerably within about 90 s (B), in parallel with a good clinical response (symptoms subsided). EEG is showed here in longitudinal bipolar montage. Supplementary material 3 shows the same EEG segments in common average montage. The patient was diagnosed with cryptogenic generalised epilepsy.

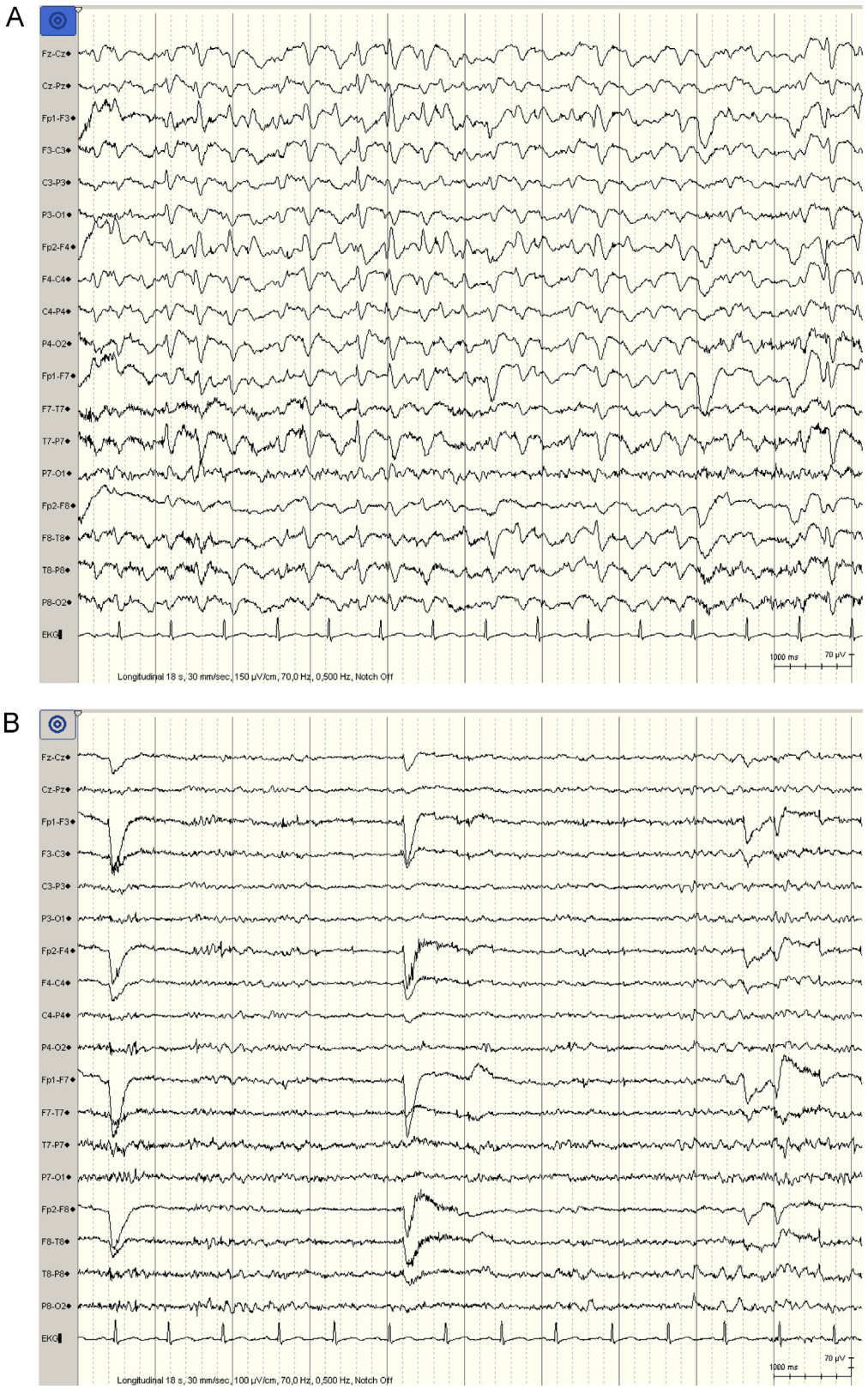


**Fig. 3.** Continuous rhythmic 1.5–2.5 Hz spike-and-slow-wave paroxysms, lasting for up to 45 min; this activity was almost always fronto-temporal with shifting side preponderance, or bifrontal synchronous (A). EEG became normalised after cessation of symptoms (B). EEG is showed here in longitudinal bipolar montage. Supplementary material 4 shows the same EEG segments in common average montage. The patient has symptomatic focal epilepsy (bilateral mesial temporal sclerosis).

embarrassing or potentially dangerous epileptic seizures by administering emergency medication in a situation where loss of control is absent or only partial.

## Conclusion

Our results suggest that in at least a part of the patients, prodromes are actually long-duration manifestations of simple partial seizures.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2013.03.013.

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